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EXAMINER
HA, JULIE

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
12/21/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/529,203	BAUER ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10,12-14,16-18,29,30,32-33,35-38,40,42-57* is/are pending in the application.

4a) Of the above claim(s) *50-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10,12-14,16-18,29,30,32,33,35-38,40,42-49 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/25/2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 01, 2009 has been entered. Claims 19-28, 34, 41 and 58-60 have been cancelled. Claims 1, 10, 12-14, 16-18, 29, 30, 32-33, 35-38, 40, 42-57 are pending in this application. Claims 50-54 remain withdrawn from further consideration, as being drawn to nonelected invention. Claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-38, 40, 42-49 and 55-57 are examined on the merits in this office action.

Maintained Rejection

35 U.S.C. 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-37, 43-49 and 55-57 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gefter et al (US Patent No. 6,180,608) in view of Bauer et al (PG Pub 2002/039996).

6. Gefter et al teach pharmaceutical compositions comprising a stable water-insoluble complex composed of a peptidic compound, preferably a pharmaceutically active peptidic compound, and a carrier macromolecule that allows for sustained delivery of the peptidic compound in vivo upon administration of the complex. The reference further teaches that the complex can permit continuous delivery of a pharmaceutically active peptidic compound to a subject for prolonged periods of time, e.g., one month, two months, three months and the like (see column 1, lines 43-52 and column 6, lines 12-13). Furthermore, the reference teaches that the complex is formed by combining the peptidic compound and the carrier macromolecule under conditions

such that a substantially water-insoluble complex is formed, e.g., aqueous solutions of the peptidic compound and carrier macromolecule are mixed until the complex precipitates. The complex may be in the form of a solid (e.g., a paste, granules, a powder or a lyophilisate)…can be pulverized finely enough to form stable liquid suspensions or semi-solid dispersions (see column 1, lines 57-65). This reads on claim 33 and claim 36 in part. The reference further teaches that the peptidic compound of the water-insoluble complex is an LHRH analog, and LHRH antagonist (see column 1, lines 66-67 and column 2, line 1). Furthermore, the reference teaches that the complex is suitable for sterilization, such as by gamma irradiation or electron beam irradiation, prior to administration *in vivo* (see column 2, lines 3-5). This reads on claims 36 and 37. Further, the reference teaches a method for treating a subject for a condition (prostate cancer) treatable with an LHRH analog by administering to the subject an LHRH-analog-containing composition (see column 2, lines 6-11). This reads on claims 48-49. The LHRH analogs are LHRH antagonists, and include antide, Cetrorelix and the like (see column 4. lines 6-27). The reference further discloses that multivalent cationic peptidic compound and multivalent anionic peptidic compound refer to peptidic compound comprising a multiplicity of positive or negative charges (see column 3, lines 46-49). Furthermore, the reference teaches that the pharmaceutical formulations comprise additional pharmaceutically acceptable carriers and/or excipients…the carrier is suitable for intravenous, intramuscular, subcutaneous or parenteral administration (e.g., by injection) (see column 7, lines 65-67 and column 8, lines 1-7). This reads on claim 43. The reference further teaches that a non-limiting range of an LHRH analog is

0.01 mg to 10 mg/kg (see column 10. lines37-38) and Examples 2-4 discloses 25 mg of peptidic compound dissolved in water (Example 2), 50 mg of peptidic compound dissolved in mannitol and carboxymethylcellulose (Example 3) and 25 mg of peptidic compound dissolved in water and added to sodium alginate (Example 4). This reads on claims 16-18. The reference further teaches that the reconstitution vehicle to be used in clinical studies is 0.9% sodium chloride (see Example 14). This reads on claims 12-14 and 27. The difference between the reference and the instant claims are that the reference does not teach D-63153, and additionally pharmaceutically active ionic peptide compound and differing NaCl concentrations of 0.05 to 0.5% (weight/volume) and 0.1 to 0.2%.

7. However, Bauer et al disclose a pharmaceutical administration forms suitable for parenteral administration, which contains peptides prone to aggregation in the form of their acetate, gluconate, glucuronate, lactate, citrate, ascorbate, benzoate, or phosphate salts in dissolved or dispersed form (see abstract). Furthermore, the reference discloses that the pharmaceutical administration forms can be present in dissolved or dispersed form in water or in aqueous solvent mixtures (see paragraph [0012]). Additionally, the reference discloses that the peptides employed are LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix and the antagonists according to the U.S. Patent # 5942493 and DE 19911771.3. (see paragraph [0014] and US Patent No. 7,005,418, column 3, lines 53-58). D-63153 is an antagonist disclosed in DE 19911771.3. Furthermore, the reference discloses that preparation of sterile solutions of LHRH antagonist for parenteral administration is by

means of filtration, especially at high concentration (see paragraph [0009]). Additionally, the reference discloses that the administration of pharmaceutically active peptides is the parenteral pharmaceutical form…in the form of reconstituted lyophilisates of soluble peptide salts and to microparticles, microcapsules or implants (see paragraph [0010]). Furthermore, the reference discloses that area of use of the preparations is in the prevention and therapy of all sex hormone-dependent conditions and diseases, which can be influenced by LHRH agonist and antagonists…benign prostate hyperplasia, carcinoma of the prostate, precocious puberty, hirsutism, endometrial hyperplasia, uterine myomatosis, breast cancer, etc (see paragraphs [0020] and [0021] and claims 16 and 17). Furthermore, the reference discloses rat animal experiment (see paragraph [0041] and Tables 8a, 8b and 9). Please note that the reference discloses the disorders that are claimed in claims 50-53 of instant application.

8. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Gefter et al and Bauer et al because both prior arts teach pharmaceutical gel formulation incorporating GnRH antagonist. There is a motivation to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist and one would expect the same activity. There is a reasonable expectation of success to substitute D-63153 for other GnRH antagonist, since both prior arts disclose Antide and Cetrorelix as examples of GnRH antagonists that can be formulated into composition in an aqueous solvent. Further, there is a reasonable expectation of success since 0.9% sodium chloride is used to reconstitute for clinical studies (see Example 14 of patent ‘608) and sustained delivery formulation for administering

pharmaceutically active peptides *in vivo* continuously for prolonged time periods are achieved by patent '608. The references are silent as to the range of NaCl concentrations.

9. However, the MPEP states the following: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. *"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."* In re Aller, *220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)* (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*"); In re Hoeschele, *406 F.2d 1403, 160 USPQ 809 (CCPA 1969)* (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re

Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Therefore, there is a reasonable expectation of success to optimize the NaCl concentration, since "*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."* One of ordinary skill in the art would have been motivated to optimize the NaCl range with for the expected benefit of at least increasing the clinical utility of the pharmaceutical preparation.

10. Furthermore, the MPEP states the following: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that

each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant."). Therefore, there is a reasonable expectation of success to add in another pharmaceutically active ionic peptide compound in a pharmaceutical gel preparation comprising D-63153, since the above mentioned compounds (such as cetrorelix) are all GnRH antagonist that are used for the same purpose, thus addition of another GnRH antagonist would at least have an additive effect.

Response to Applicant's Arguments

11. Applicant argues that "Gefter et al disclose a pharmaceutical composition comprising a water-insoluble complex composed of a peptidic compound and a macromolecule carrier that allows for sustained release of the peptidic compound *in vivo*. The peptidic compound of Gefter et al comprise an LHRH analogue which may be an LHRH agonist or an LHRH antagonist in a narrower sense, including the exemplary the LHRH antagonists PPI-149, PPI-258 and cetrorelix. In Gefter et al, the carrier macromolecule comprises cationic carrier macromolecule like ply-L-lysine and other polymers of basic amino acids or anionic carrier macromolecule like polyalcohol derivatives, specifically polysaccharides and more specifically carboxymethylcellulose,

algin, alginate, acetate polymers, acrylic polymers, alkali starch glycolate and others. The current invention does not comprise a carrier macromolecule and does not use such carrier macromolecule. On the contrary the inventive peptide forms the administration form for sustained release itself."

Applicant further argues that "Gefter et al use a 0.9% sodium chloride in Example 14 as a reconstitution vehicle to reconstitute the complex PPI-149-CMC, consisting of the peptidic compound PPI-149 and the macromolecule carboxymethylcellulose, wherein the complex PPI-149-CMC is already a sustained delivery complex. However, the present invention uses sodium chloride as an inorganic salt as the reconstitution medium and to prepare a sustained release form from an easily soluble peptide or peptide salt."

Further, Applicant argues that "Bauer et al discloses that peptide have a nature prone to uncontrolled aggregation and that the peptides if administered lead to a concentration-dependent lowering of the bioavailability form the peptide concentration. Bauer et al therefore disclose that the addition of a free acid to the easily soluble peptide salt prevents that peptide salts prone to aggregation." Applicant argues that "Bauer et al does not actually disclose or suggest D-63153. U.S. Patent No. 5,942,493 and DE 19911771.3 references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed." Furthermore, Applicant argues that "Bauer et al disclose a pharmaceutical administration form which contains peptides prone to aggregation. Bauer et al provide a teaching to avoid aggregation of the

peptides whereas the presently claimed invention is a sustained release formulation and consequently involves the aggregation of peptides by reconstitution of lyophilized peptide salts with inorganic salts or acetic acid salts. Thus, the mechanism by which the claimed invention is achieved as compared to the cited are at direct odds and are incompatible. Therefore, Applicants submit that the teachings of Bauer et al are not relevant to the claims of the present application. It is only when Applicants disclosure is used as a guidepost to reconstitute the claimed invention with the benefit of hindsight that the disclosure of Gefter et al and Bauer et al are combinable."

Applicant further argues that "Examples 1 to 7 describe numerous examples where D-63153 is reconstituted in 0.1% to 0.2% sodium chloride. In Example 2, D-63153 reconstituted in 0.1% sodium chloride is shown to retain absolute bioavailability…Examples 4-7 provide various viscosity studies with D-63153 reconstituted in 0.1% to 0.2% sodium chloride, with Example 7 illustrating the clear advantages obtained by reconstitution of D-63153 in sodium chloride."

12. Applicant's arguments have been fully considered but have not been found persuasive. Gefter et al teach the GnRH (LHRH) antagonist such antide and cetrorelix and a carrier molecule for sustained release *in vivo*. In regards to Applicant's argument that instant invention "does not comprise a carrier macromolecule and does not use such carrier macromolecule", Applicant is reminded that the claim recites the transitional phrase "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps (see MPEP 2111.03). Therefore, other elements may be included in the claimed language. Further, Gefter reference teaches the

reconstitution of the GnRH antagonist in 0.9% NaCl for clinical utility. Since the sustained release form of PPI-149 is being reconstituted in the same NaCl solution, this meets the limitation of the claims.

Bauer reference teaches that pharmaceutically active decapeptides (cetrorelix) in the form of their pharmaceutically acceptable, non-toxic acid addition salts such as hydrochlorides…acetates, citrates…etc (see paragraph [0002]). Further, Bauer discloses pharmaceutical administration forms suitable for parenteral administration, which contains peptides prone to aggregation in dissolved or dispersed form and the peptides are present in the form of their acetate salts. Further, Bauer discloses that the administration of pharmaceutically active peptides is the parenteral pharmaceutical form…in the form of reconstituted lyophilisates of soluble peptide salts and to microparticles, microcapsules or implants (see paragraph [0010])…and the pharmaceutical administration forms contain peptides prone to aggregation in dissolved or dispersed form, wherein the peptides are present in the form of their acetate and other salts and these administration forms can additionally contain one of the acids as free acids (see paragraph [0011]). The Bauer reference teaches the LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix and the antagonists according to the U.S. Patent # 5942493 and DE 19911771.3 in dissolved form, for parenteral administration. Bauer discloses that area of use of the preparations is in the prevention and therapy of all sex hormone-dependent conditions and diseases. Furthermore, both prior arts teach pharmaceutical gel formulation incorporating GnRH antagonist. Additionally, the instant claims recite, "a mixture of D-

63153 in lyophilized form and an aqueous solution of an inorganic or acetic acid at a concentration of from 0.05% to 0.5%." A solubilized peptide can be in a pharmaceutical gel preparation. Gefter reference teaches GnRH antagonist in NaCl solution, and Bauer et al disclose LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix and the antagonists according to the U.S. Patent # 5942493 and DE 19911771.3 in solubilized form for parenteral administration.

There is a motivation to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist and one would expect the same activity. In regards to Applicant's argument that Bauer et al does not actually disclose or suggest D-63153. U.S. Patent No. 5,942,493 and DE 19911771.3 references disclose a large number of peptides, one of which is D-63153. However, Bauer et al or these references fail to provide any specific motivation to select D-63153 for use as presently claimed." As indicated above in the body of the rejection, U.S. Patent No. 7,005,418 indicates that the antagonist can also be the LHRH antagonist D-63153 as described in the German Patent Application No. 199 11 771.3 (see column 3, lines 53-57). A large number of peptide antagonists is provided and known in the art. The one of ordinary skill in the art can pick and choose any known antagonist. The KSR states the following: It has been held that under KSR that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in KSR, When there is motivation "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and

common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727,_,82 USPQ2d 1385, 1397 (2007).

The "problem" facing those in the art was developing a sustained release formulation comprising GnRH antagonist, and there were a limited number of peptide antagonists and methodologies available to do so, for example Cetrorelix, teverelix, abarelix, ganirelix, azaline B, antide, detirelix, ramorelix, degarelix, D-63153, Nal-Glu, antarelix etc. Gefter teaches GnRH antagonist reconstituted in 0.9% NaCl for clinical studies. The skilled artisan would have had reason to try any GnRH antagonist and methodologies with the reasonable expectation that at least one would be successful. The GnRH antagonists are well known in the art. Thus, pharmaceutical formulation comprising any one of GnRH antagonist in an aqueous solution of inorganic salt is a "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

Additionally, since the claims do not further limit the structural attributes of the pharmaceutical gel preparation, and since the prior arts teach the peptides having these limitations in pharmaceutical gel preparations, the process of making (mechanism of how the product is achieved) still would not limit the structural attributes. The pharmaceutical preparation of the combined prior art comprise the GnRH/LHRH antagonist and the NaCl solution. Therefore, one would be motivated to optimize the pharmaceutical gel preparation by optimizing the peptide concentration and NaCl concentration. Therefore, there is a reasonable expectation of success to optimize the

NaCl concentration, since "*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*" One of ordinary skill in the art would have been motivated to optimize the NaCl range with for the expected benefit of at least increasing the clinical utility of the pharmaceutical preparation.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In regards to Applicant's argument "Examples 1 to 7 describe numerous examples where D-63153 is reconstituted in 0.1% to 0.2% sodium chloride…with Example 7 that illustrating the clear advantages obtained by reconstitution of D-63153 in sodium chloride." Gefter et al teach the GnRH antagonist reconstituted in 0.9% NaCl for clinical use. Applicant has not shown any data comparison of differing NaCl concentrations and its effect on the blood plasma, the viscosity and so on. The only data shown are for those in 0.1% NaCl concentration. The data cannot be compared, since the data only shows using 0.1% NaCl only. It cannot be determined if there is any

advantage or beneficial effect or unexpected results, since the only data shown is for 0.1% NaCl and not for different NaCl concentrations.

Therefore, the prior arts are obvious over claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-37, 43-49 and 55-57.

13. Claims 38, 40 and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gefter et al (US Patent No. 6,180,608) in view of Bauer et al (US 2002/039996) as applied to claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-37, 43-49 and 55-57 above, in further view of Engel et al (US Patent No. 5,663,145).

14. The teachings of Gefter et al and Bauer et al are described, *supra*. The difference between the references and the instant claims is that the references do not teach a kit.

15. However, Engel et al teach substances available for treating hormone-dependent malignant diseases (see column 1, lines 6-7). Engel teaches that Cetrorelix (INN) is an antagonist for LHRH (see column 1, line 15). Engel teaches that in clinical trials, a daily dose of 10 mg showed a complete suppression of the hormone concentration to castration level (see column 1, lines 20-22). Additionally, Engel teaches the dosage regimen of the pharmaceutical composition: an initial dose with the amount of 1-60 mg in a lyophilisate ampoule or several lyophilisate ampoules; lyophilisate ampoules in a slow-release form with a rate of delivery of 0.1-10 mg/day for the whole period of treatment; or lyophilisate ampoules which contain the amount of active substance, which is not in a slow-release form, in an amount of 0.1-10 mg (see column 1, lines 42-

54). The reference further teaches the aseptic procedures and lyophilizing the Cetrorelix solution (see column 2, lines 24-40). Furthermore, the reference teaches a kit comprising LHRH antagonist, Cetrorelix (see claims 1-3) and the method of treating a hormone-dependent condition (prostate cancer) comprising administering LHRH antagonist (Cetrorelix) (see claims 7 and 13).

16. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Gefter and Bauer and Engel because the prior arts teach the pharmaceutical formulation of GnRH antagonists in liquid form. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. Bauer further discloses D-63153 as one of the peptides employed (see paragraph [0014] and see US Patent No. 7,005,418, column 3, lines 53-58). One of ordinary skill in the art would be motivated to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist according to the prior arts, and thus, one would expect the same activity. There is a reasonable expectation of success since the Bauer and Engel teach the use of the formulation for the treatment of hormone-dependent disorder, specifically prostate cancer. Furthermore, there is a reasonable expectation of success since GnRH antagonists have similar properties, such as solubility, and are used to treat the same disorder.

Response to Applicant's Arguments

17. Applicant argues that "the presently claimed invention relates to kit comprising an LHRH antagonist as a finished preparation of the peptide compound and a solution of an inorganic salt or acetic acid salt for reconstitution." Applicant argues that "a combination of teachings of Gefter et al, Bauer et al and Engel et al would not directly lead a person skilled in the art to the subject matter of the aforementioned kit claims neither to any other amended claims as proposed herein for the reasons already provided." Applicant argues that "Gefter et al fails to disclose or suggest the pharmaceutical compositions of the present invention…do not disclose or suggest the importance of using an aqueous solution of sodium chloride in the reconstitution of the active ionic peptide to form a gel, or of the concentrations of such salts for this purpose (0.01 to 0.9% w/v)...Gefter et al do not disclose or suggest D-63153 or the concentrations of sodium chloride used for reconstituting it." Applicant further argues that "the presently claimed invention relates to kit comprising an LHRH antagonist as a finished preparation of the peptide compound and a solution of sodium chloride for reconstitution...a combination of the teaching of Gefter et al, Bauer et al, and Engel et al would not directly lead a person skilled in the art to the subject matter of the aforementioned kit claims neither to any other amended claim as proposed herein for the reasons already provided above." Applicant further argues that "Engel et al disclose a dosage regimen of the pharmaceutical composition in which lyophilisate ampoules are in the form of an acetate and it is not intended to bring it in a slow release form in an embonate salt".

18. Applicant's arguments have been considered but have not been found persuasive because all three cited prior arts teach the pharmaceutical formulation of GnRH antagonists in liquid form. Furthermore, Gefter et al teaches that the GnRH (LHRH) antagonist is in solid form (lyophilisate) and reconstituted in NaCl for clinical purposes. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. Gefter et al teach the GnRH (LHRH) antagonist such antide and cetrorelix and a carrier molecule for sustained release *in vivo*. Further, Gefter reference teaches the reconstitution of the GnRH antagonist in 0.9% NaCl for clinical utility. Since the sustained release form of PPI-149 is being reconstituted in the same NaCl solution, one would be motivated to try reconstitution other GnRH/LHRH antagonist in the same aqueous solution. Gefter et al teach the GnRH antagonist reconstituted in 0.9% NaCl for clinical use. Applicant has not shown any data comparison of differing NaCl concentrations and its effect on the blood plasma, the viscosity and so on. The only data shown are for those in 0.1% NaCl concentration. The data cannot be compared, since the data only shows using 0.1% NaCl only. It cannot be determined if there is any advantage or beneficial effect or unexpected results, since the only data shown is for 0.1% NaCl and not for different NaCl concentrations.

Bauer reference teaches that pharmaceutically active decapeptides (cetrorelix) in the form of their pharmaceutically acceptable, non-toxic acid addition salts such as hydrochlorides…acetates, citrates…etc (see paragraph [0002]). Further, Bauer discloses pharmaceutical administration forms suitable for parenteral administration,

which contains peptides prone to aggregation in dissolved or dispersed form and the peptides are present in the form of their acetate salts. Further, Bauer discloses that the administration of pharmaceutically active peptides is the parenteral pharmaceutical form…in the form of reconstituted lyophilisates of soluble peptide salts and to microparticles, microcapsules or implants (see paragraph [0010])…and the pharmaceutical administration forms contain peptides prone to aggregation in dissolved or dispersed form, wherein the peptides are present in the form of their acetate and other salts and these administration forms can additionally contain one of the acids as free acids (see paragraph [0011]). The Bauer reference teaches the LHRH antagonists antide, A-75998, ganirelix and Nal-Glu antagonist, but in particular cetrorelix, antarelix and the antagonists according to the U.S. Patent No. 5,942,493 and DE 19911771.3 in dissolved form, for parenteral administration. Bauer discloses that area of use of the preparations is in the prevention and therapy of all sex hormone-dependent conditions and diseases. Furthermore, both prior arts teach pharmaceutical gel formulation incorporating GnRH antagonist. Bauer further discloses D-63153 as one of the peptides employed (see paragraph [0014] and see US Patent No. 7,005,418, column 3, lines 53-58). One of ordinary skill in the art would be motivated to substitute D-63153 for other GnRH antagonists since they are all recognized GnRH antagonist according to the prior arts, and thus, one would expect the same activity. There is a reasonable expectation of success since the Bauer and Engel teach the use of the formulation for the treatment of hormone-dependent disorder, specifically prostate cancer. Furthermore, there is a reasonable expectation of success since GnRH antagonists have similar properties,

such as solubility, and are used to treat the same disorders. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. The instant claims do not further limit the structural attributes of the pharmaceutical gel preparation, and Engel et al teach the dosage regimen: an initial dose with the amount of 1-60 mg in a lyophilisate ampoule or several lyophilisate ampoules; lyophilisate ampoules in a slow-release form with a rate of delivery of 0.1-10 mg/day for the whole period of treatment; or lyophilisate ampoules which contain the amount of active substance, which is not in a slow-release form, in an amount of 0.1-10 mg (see column 1, lines 42-54) and furthermore, teach a kit comprising the LHRH antagonist. Engel et al teach the kit comprising dosage in lyophilisate ampoules (see claims 4-5) and in slow-releasing formulation (see claim 6). Since the Gefter teaches that for clinical use, NaCl is used to reconstitute the lyophilisate, it would be obvious to one of ordinary skill in the art to include a NaCl solution in the kit for reconstitution purposes.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Gefter and Bauer and Engel because the prior arts teach the pharmaceutical formulation of GnRH/LHRH antagonists in pharmaceutical form. All three prior arts teach the method of treating a hormone-dependent condition (prostate cancer) by administering a pharmaceutical composition of Cetrorelix. Bauer further discloses D-63153 as one of the peptides employed (see paragraph [0014] and see US Patent No. 7,005,418, column 3, lines 53-58). One of ordinary skill in the art would be motivated to substitute D-63153 for other GnRH antagonists since they are all

recognized GnRH/LHRH antagonist according to the prior arts, and thus, one would expect the same activity. There is a reasonable expectation of success since the Bauer and Engel teach the use of the formulation for the treatment of hormone-dependent disorder, specifically prostate cancer. Furthermore, there is a reasonable expectation of success since GnRH/LHRH antagonists have similar properties, such as solubility, and are used to treat the same disorders. Therefore, the prior arts combined meets the limitations of claims 1, 10, 12-14, 16-18, 29-30, 32-33, 35-38, 40, 42-49 and 55-57.

New Objection

19. The figures are objected to for the following reasons: The figures comprise multiple data sets that have not been labeled. For example, Fig. 3 shows two data sets, but it is not clear if they represent duplicate experiments or each data is for independent experiments (for example, different concentrations of NaCl) Figs. 4 and 5 show three data sets, but it is not clear if they represent triplicate experiments or each data is for independent experiments (for example, different concentrations of NaCl). Applicant is required to submit a new drawing which clearly label or explain each data set.

20. Figs. 4 and 5 also indicate that 65 mg D-65153 was dissolved in 2.6 nl 0.1% NaCl solution. However, right below the description (above the graph), the description reads: "...65 mg D-65153 dissolved in 2.6 ml 0.1% NaCl solution..." The Example 7 description discloses that D-65153 were produced and reconstituted with 2.6 ml of a 0.1% strength NaCl solution…" (see paragraph [0103] of instant specification US 2005/0282731 A1). These errors should be corrected.

Conclusion

21. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Julie Ha/
Examiner, Art Unit 1654